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Research Article

Comparative study for efficacy of termination in first trimester pregnancy using Misoprostol and Mifepristone

Abstract

Background: The best method for medical abortion depends fundamentally on pregnancy duration and the final result varies on medical staff's experience. The aim of this study pertained to investigate the effectiveness of medical abortion using misoprostol, mifepristone or the combination of them.

Patients and methods: During the period April 2007 to December 2017, 200 women with pregnancy until 49 days after LMP (last menstrual period) underwent medical termination by using 600 mg mifepristone (RU 486) (Mifegyn) Group A1 per os vs 800 mcg misoprostol (Cytotec) A2 and in other 200 pregnant women, duration between 49-63 days was administrated using 600 mg mifepristone followed 48 hours later 800 mcg misoprostol B1 vaginally vs. only misoprostol B2. All participants were consistent with surgical abortion if deemed necessary and a transvaginal ultrasound was performed to confirm an intrauterine pregnancy before the medical administration. The indications for the abortion were as following: missed abortion, endometrial death, spontaneous and induced abortions.

Results: According to our study, there was not a case needed to undergo surgical abortion. Common side effects like nausea, vomiting, pain and moderate vaginal bleeding were noticed without the need of hospitalization. Bleeding was occurred earlier in Group A1 compared to Group A2. In addition, abortion started about 3.5 hours earlier in Group A1 compared to Group A2. Similarly, time between administration and abortion was 50% shorter in Group A1 compared to Group A2. The duration of bleeding in Group B1 in Group B2 was similar in the two groups. Analgesia was not necessary for any participant, while repeat administration was more than 7 times more frequent in Group B2 compared to Group B1.

Conclusion: The combination of mifepristone and misoprostol and the single administration of mifepristone are safe and effective for medical termination of pregnancy in early first trimester.

Introduction

The induced abortion rate is associated to a variable reported incidence, lower in countries with satisfactory organized family planning services and higher in poor societies when social and economic pressures led the people to reach their fertility goals through the availability of natural family planning contraception's methods resulting unintended pregnancies [1,2]. The estimated abortion rate around the world referred average by 3.5% [3]. Epidemiological studies consulted to the confirmation that the human reproductive system is finely tuned to produce a minimum optimum interval between pregnancies. If pregnancy occurs in this time interval due to not using contraception's methods is associated to improving infant and maternal mortality and morbidity [4]. The management of unwanted pregnancies and the subsequent contraception shas a great meaning for the concerning women

especially the teenagers which should be educated regarding the contraception's options to protect their fertility. The major challenge in the present time remains to ensure the effective methods of inducing abortion widely and make available to majority of women in the world. The induced abortion rate beyond the 1st trimester is less than 15% of all refer procedures in the world and especially in European area ranged between 2 and 10%. Unfortunately was estimated that about twenty two million unsafe abortions were performed every year and 98% appear in developing countries [5-7]. Unsafe abortion is defined as a pregnancy termination in which the women underwent lacking and not conform to minimal recommend medical standards [5,6]. As part of improving maternal health and international development goals and targets unsafe abort must be dealt to prevent maternal mortality and morbidity [7]. The health consequences of unsafe abortion are based on the method of abortion used, gestational age and finally

skills of the abortion provider [8]. Although contraceptive use led to reduce the number of unintended pregnancies, however approximately 33 million contraceptive users report about accidental pregnancy. Approximately 85 million (41%) women from 208 million total which estimated to be pregnant each year worldwide were noticed as unintended [9–11]. The recommend medical method for induced abortion include mifepristone alone or in combination with misoprostol [12–20]. To investigate the effectiveness and safety of pregnancy termination as medical abortion based pharmacological procedure without hospital stay.

Patients and Methods

All participants were consistent with surgical abortion if deemed necessary and a transvaginal ultrasound was performed to confirm an intrauterine pregnancy before the medical administration. In the upper described protocol first trimester pregnancies until 9 weeks or 63 days gestational age since the 1st day of the last menstrual period are included, for medical termination. The indications for the abortion were as following: missed abortion, embryonic demise, spontaneous and induced abortions. We obtained approval by the institutional ethics committee and all eligible patients gave their written consent after receiving relevant information including the potential adverse effects of medical pregnancy termination. Four hundred eligible participants were selected from the hospital medical records total seven hundred young pregnant women, who visited the family planning centre Democritus University of Thrace, Greece for abortion induction in the study time. Data were extracted by chart review that included patient information. All patients had signed a written consent after detailed information about abortions induction modus. Pregnant women were arranged in two groups. The group A includes pregnant women until 49 days after LMP in which pregnancy termination will be performed either with four tablets (800 mcg) Misoprostol placed in the posterior vaginal fornix or three tablets (600mg) Mifepristone administrated orally. In the group B were enrolled pregnant women with gestational age between 49 until 63 days in which the pregnancy termination procedure was performed using either the combination of Mifepristone and Misoprostol or Misoprostol alone (Figure 1). In cases of medical combination three tablets Mifepristone (600mg) were taken orally on first day and 48 hours following ingestion of Mifepristone, 800 mg Misoprostol were placed vaginally in the participants (Figure 1). To investigate the effectiveness of the two medical methods of pregnancy termination in first trimester were examined and evaluated the following control parameters like as: Start bleeding in the two main groups, start the abortion in the two main groups, completion of abortion in major groups certified after seven days with transvaginal ultrasound, necessity of surgical abrasion or aspiration after drug abortion due to fetal remnants, recording of side effects (fever, major bleeding, vomiting, nausea, blood transfusion) in the two main groups, effect on the menstrual cycle for three months after the medical abortion certified with a questionnaire and ultrasound checks once a month at the Outpatient Clinic of the Family Planning of the DUTH. Exclusions criteria were the following: reproductive tract infections, presence of sexually transmitted

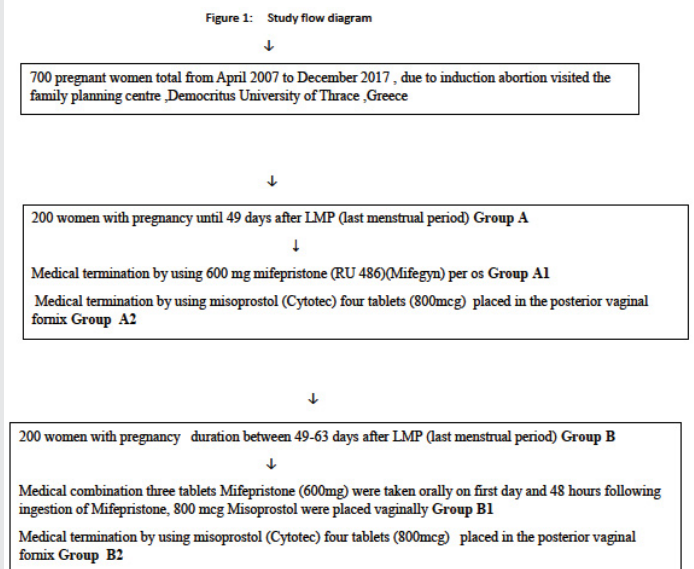


Figure 1:

infections, medical allergy to induction drugs, history of severe diseases like adrenal or liver failure, severe anemia, inherited porphyria, cardiovascular risk factors. Previously performed uterine surgical interventions and multifetal pregnancies were enrolled in our study, however needed special attention during the induced abortion and in the post procedure period. Success of medical procedure was defined as the non-surgical evacuation of the products of conception, including: a) complete abortion without remains and b) incomplete abortion with different amounts of remains that were expelled with the additional doses of misoprostol. Failure was defined as the conversion of medical to surgical abortion, in the cases of incomplete abortion. Surgical intervention was indicated because of failure of the medical induced abortion, excessive bleeding, persistent products of conception 5 weeks later, or other serious medical conditions.

Statistical analysis

Statistical Package for the Social Sciences (SPSS), version 19.0 (IBM) was used for statistical analysis. The normality of quantitative variables was examined with Kolmogorov-Smirnov test. All quantitative variables were determined as the mean $\pm$ standard deviation (SD). Categorical variables were determined as frequencies (and percentage). Student's t test and chi-square test were used to determine differences between two groups of patients. Odds ratios (OR) and their 95% confidence interval (CI) were estimated by mean of logistic regression models as a measure of association between categorical variables. All assays were two tailed and statistical significance was considered for p values less than 0.05.

Results

Sample

From the entire cohort of all women who underwent medical termination during the period from April 2007 to December 2017, 200 women Group A with pregnancy until

49 days after LMP (last menstrual period) and 200 women Group B with pregnancy between 49–63 days were randomly selected using the systematic random sampling method. The gestational age of women in Group A ranged from 36 to 49 days with a mean of 43.88 ± 3.15 days (median, 45 days) while in Group B ranged from 50 to 63 days with a mean of 57.97 ± 3.05 days (median, 58 days) ($p < 0.001$). Regarding women's age, it was ranged from 13 to 43 years with a mean value of 23.48 ± 5.29 years (median, 24 years) in Group A while in Group B was ranged from 14 to 46 years with a mean of 22.50 ± 5.04 years (median, 22.5 years) ($p = 0.057$).

Women with pregnancy until 49 days

Women's characteristics: Pregnant women of Group A (women with pregnancy until 49 days) underwent medical termination by using either 600 mg mifepristone per os (Group A1) or 800 mcg misoprostol vaginally (Group A2). There were no statistically significant differences between the two groups in age (Group A1: mean 22.89 ± 4.78 years, range 15–37 years, median 23 years; Group A2: mean 23.96 ± 5.64 years, range 13–43 years, median 24 years; $p = 0.153$) and gestational age (Group A1: mean 43.97 ± 3.11 days, range 36–49 days, median 45 days; Group A2: mean 43.81 ± 3.19 days, range 36–49 days, median 44 days; $p = 0.730$) (Table 1).

The two groups were also similar in terms of height ($p = 0.975$) and weight ($p = 0.893$) (Table 1). The vast majority of women in both groups were primipara (Group A1: 74.2%; Group A2: 82.0%) and null gravidity and parity (Group A1: 87.6%; Group A2: 93.7%). There were no statistically significant differences in the number of previous pregnancies ($p = 0.270$), the number of previous deliveries ($p = 0.137$) and the prevalence of missed abortion ($p = 0.137$) between the two groups of women (Table 1). Finally, the distribution of women according to education level and to social status was similar in both groups ($p = 0.669$ and $p = 0.445$, respectively) while the majority of women in both groups were smokers (Group A1: 59.6% vs Group A2: 58.6%, $p = 0.887$).

Control parameters in relation to medication

Several control parameters and criteria for the evaluation of the effectiveness of medication pregnancy termination were compared between the groups A1 and A2. After medicine administration, bleeding occurred 0.28 hours (or 14.1%) earlier in Group A1 compared to Group A2 (1.70 ± 0.88 hours vs 1.98 ± 0.81 hours, $p = 0.019$). In addition, abortion started about 3.5 hours (or 46.5%) earlier in Group A1 compared to Group A2 (4.27 ± 7.98 hours vs 7.98 ± 1.56 hours, $p < 0.001$). Similarly, time between administration and abortion was 50% shorter in Group A1 compared to Group A2 (1.21 ± 0.49 hours vs 2.42 ± 0.94 hours, $p < 0.001$) (Table 2). The duration of bleeding (2.07 ± 0.77 days in Group A1 vs 2.23 ± 0.76 days in Group A2, $p = 0.147$) was similar in the two groups. Analgesia and extra administration were not necessary for any participant as shown in (Table 2). Side effects (fever, vomiting, nausea, blood transfusion, diarrhea, dizziness, fatigue, headache, breast tenderness) were similar in the two groups (all $p > 0.05$) (Table 3).

Table 1: Group A (≤ 49 DAYS)

	MIF (Group A1)	C (Group A2)	p value
Age (years)	22.89 ± 4.78	23.96 ± 5.64	0.153
Gestation age (weeks)	43.97 ± 3.11	43.81 ± 3.19	0.730
Height (cm)	164.52 ± 8.38	164.98 ± 7.78	0.685
Weight (kg)	72.06 ± 7.94	73.78 ± 8.16	0.136
Missed abortion (no, %)	11 (12.4%)	7 (6.3%)	0.137
Number of previous pregnancies (no, %)			0.270
None	66 (74.2)	91 (82.0)	
One	12 (13.5)	9 (8.1)	
Two	9 (10.1)	6 (5.4)	
Three or more	2 (2.2)	5 (4.5)	
Number of previous deliveries (no, %)			0.137
None	78 (87.6)	104 (93.7)	
One or more	11 (12.4)	7 (6.3)	
Education level (no, %)			0.669
Low	2 (2.2)	5 (4.5)	
Medium	61 (68.5)	76 (68.5)	
High	26 (29.3)	30 (27.0)	
Social status (no, %)			0.445
Low	0 (0)	2 (1.8)	
Medium	41 (46.1)	50 (45.0)	
High	48 (53.9)	59 (53.2)	
Smoking (no, %)	53 (59.6%)	65 (58.6%)	0.887

Table 2: Group A (≤ 49 DAYS)

	MIF (Group A1)	C (Group A2)	p value
Bleeding begin (hours)	1.70 ± 0.88	1.98 ± 0.81	0.019
Abortion (hours)	4.27 ± 0.56	7.98 ± 1.56	<0.001
Timing ... abortion (hours)	1.21 ± 0.49	2.42 ± 0.94	<0.001
Curettage (no, %)	0 (0%)	0 (0%)	1.000
Days of bleeding	2.07 ± 0.77	2.23 ± 0.76	0.147
Analgesia (no, %)	0 (0%)	0 (0%)	1.000
Repeat administration (no, %)	0 (0%)	0 (0%)	1.000
More than one clinic visits (no, %)	0 (0%)	0 (0%)	1.000
Anembryonic (no, %)	7 (7.9%)	13 (11.7%)	0.368
Ongoing pregnancy (no, %)	77 (86.5%)	94 (84.7%)	0.715

Table 3: Group A (≤ 49 DAYS)

	MIF (Group A1)	C (Group A2)	P value
Side effects (no, %)			
Fever	0 (0%)	0 (0%)	1.000
Vomiting	3 (3.4%)	3 (3.4%)	1.000
Nausea	3 (3.4%)	3 (3.4%)	1.000
Blood transfusion	0 (0%)	0 (0%)	1.000
Diarrhea	3 (3.4%)	7 (6.3%)	0.344
Dizziness	0 (0%)	0 (0%)	1.000
Fatigue	3 (3.4%)	8 (7.2%)	0.237
Headache	0 (0%)	0 (0%)	1.000
Breast tenderness	0 (0%)	0 (0%)	1.000

Women with pregnancy more than 49 days

Women's characteristics: Pregnant women of Group B (women with pregnancy more than 49 days) underwent medical termination by using either combination of 600 mg mifepristone per os and 48 hours later 800 mcg misoprostol vaginally Group B1 or only 800 mcg misoprostol vaginally Group B2. There were no statistically significant differences between the two groups in age, Group B1: mean 22.04 ± 5.18 years, range 14–46 years, median 22 years; Group B2: mean 23.19 ± 4.77 years, range 16–36 years, median 24 years; $p=0.115$) and gestational age (Group B1: mean 58.03 ± 2.92 days, range 50–63 days, median 58 days; Group B2: mean 57.88 ± 3.62 days, range 50–63 days, median 58 days; $p=0.721$) (Table 4). The two groups were also similar in terms of height ($p=0.075$) and weight ($p=0.607$) (Table 4). The vast majority of women in both groups were primipara (Group B1: 81.6%; Group B2: 71.2%) and null gravidity and parity (Group B1: 90.8%; Group B2: 87.5%). There were no statistically significant differences in the number of previous pregnancies ($p=0.295$), the number of previous deliveries ($p=0.451$) and the prevalence of missed abortion ($p=0.244$) between the two groups of women (Table 4). Finally, the distribution of women according to education level and to social status was similar in both groups ($p=0.622$ and $p=0.163$, respectively), while the majority of women in both groups was smokers (Group B1: 57.5% vs. Group B2: 68.8%, $p=0.108$) (Table 4).

Control parameters in relation to medication

Several control parameters and criteria for the evaluation of the effectiveness of medication pregnancy termination were compared between the two groups: B1 and B2. After medicine administration, bleeding occurred 0.34 hours (or 10.3%) earlier in Group B1 compared to Group B2 (2.97 ± 0.90 hours vs 3.31 ± 0.90 hours, $p=0.010$). In addition, abortion started about 1.2 hours (or 12.2%) earlier in Group B1 compared to Group B2 (8.81 ± 1.84 hours vs 10.03 ± 3.17 hours, $p=0.002$). Similarly, time between administration and abortion was significantly shorter (by 1.12 hours, 16.6%) in Group B1 compared to Group B2 (5.64 ± 1.84 hours vs 6.76 ± 3.27 hours, $p=0.006$) (Table 5).

The duration of bleeding (2.17 ± 1.05 days in Group B1 vs 2.10 ± 1.07 days in Group B2, $p=0.625$) was similar in the two groups. Analgesia was not necessary for any participant, while repeat administration was more than 7 times more frequent in Group B2 compared to Group B1 (20% vs. 3.3%, $p<0.001$; OR=7.25, 95% CI=2.33–22.61) (Table 5). Among possible side effects, diarrhea was more than 6 times (10% vs. 1.7%, $p=0.008$; OR=6.56, 95% CI=1.35–31.73) and fatigue more than 4 times (10% vs. 2.5%, $p=0.023$; OR=4.33, 95% CI=1.11–16.87) more frequent in Group B2 compared to Group B1 (Table 6).

Discussion

Medical abortion has been investigated as an option for premature termination of undesirable pregnancy and avoidance the risk of anesthesia, surgical injuries of cervix, uterus, other organs as well as the cases of uterine perforation (0.12–1.98%), blood transfusion (0.5%), necessity of repeating

Table 4: Group B (>49 DAYS)

MIF/C (Group B1) C (Group B2) <i>P</i> value			
Age (years)	22.04 ± 5.18	23.19 ± 4.77	0.115
Gestation age (weeks)	58.03 ± 2.92	57.88 ± 3.62	0.721
Height (cm)	165.58 ± 7.52	163.51 ± 8.62	0.075
Weight (kg)	72.88 ± 7.48	73.48 ± 8.84	0.607
Missed abortion (no, %)	14 (11.7%)	14 (17.5%)	0.244
Number of previous pregnancies (no, %)			0.295
None	98 (81.6)	57 (71.2)	
One	9 (7.5)	12 (15.0)	
Two	8 (6.7)	6 (7.5)	
Three or more	5 (4.2)	5 (6.3)	
Number of previous deliveries (no, %)			0.451
None	109 (90.8)	70 (87.5)	
One or more	11 (9.2)	10 (12.5)	
Education level (no, %)			0.622
Low	9 (7.5)	4 (5.0)	
Medium	81 (67.5)	52 (65.0)	
High	30 (25.0)	24 (30.0)	
Social status (no, %)			0.163
Low	5 (4.2)	0 (0)	
Medium	57 (47.5)	37 (46.3)	
High	58 (48.3)	43 (53.8)	
Smoking (no, %)	69 (57.5%)	55 (68.8%)	0.108

Table 5: Group B (>49 DAYS)

MIF/C (Group B1) C (Group B2)P value			
Bleeding begin (hours)	2.97 ± 0.90	3.31 ± 0.90	0.010
Abortion (hours)	8.81 ± 1.84	10.03 ± 3.17	0.002
Timing ... abortion (hours)	5.64 ± 1.84	6.76 ± 3.27	0.006
Curettage (no, %)	0 (0%)	0 (0%)	1.000
Days of bleeding	2.17 ± 1.05	2.10 ± 1.07	0.625
Analgesia (no, %)	0 (0%)	0 (0%)	1.000
Repeat administration (no, %)	4 (3.3%)	16 (20.0%)	<0.001
More than one clinic visits (no, %)	0 (0%)	0 (0%)	1.000
Anembryonic (no, %)	17 (14.2%)	7 (8.8%)	0.248
Ongoing pregnancy (no, %)	86 (71.7%)	62 (78.5%)	0.281

Table 6: Group B (>49 DAYS)

MIF/C (Group B1) C (Group B2) P value			
Side effects (no, %)			
Fever	0 (0%)	0 (0%)	1.000
Vomiting	0 (0%)	0 (0%)	1.000
Nausea	3 (2.5%)	3 (2.5%)	1.000
Blood transfusion	0 (0%)	0 (0%)	1.000
Diarrhea	2 (1.7%)	8 (10.0%)	0.008
Dizziness	0 (0%)	0 (0%)	1.000
Fatigue	3 (2.5%)	8 (10.0%)	0.023
Headache	0 (0%)	0 (0%)	1.000
Breast tenderness	0 (0%)	0 (0%)	1.000

surgical intervention (1%) and ongoing pregnancy due to failure of surgical intervention (0.2%) [19–22]. Also, the risk of adhesions of the uterus in both the endometrial cavity and the minor pelvis near the uterus is avoided by drug abortion. Disadvantages of this method are close medical monitoring, frequent control with ultrasound and biochemical parameters, prolongation of vaginal bleeding and pelvic pain.

It is a good alternative and involves avoiding surgical interruption of pregnancy by cervical dilation and vaginal scarring. It is estimated that over 50% of pregnancies in humans will not develop further and will not get the character of clinically apparent pregnancy [23]. It is also estimated that 15% of pregnancies will develop clinically but will result in what is called “spontaneous abortion” [24]. In recent years, the increased use of ultrasound in Obstetrics led to the early diagnosis of a large number of unsuccessful pregnancies during the first trimester.

Medical methods of abortion have been proved to be safe and effective. The most effective regimens include the Mifepristone and misoprostol. Gemeprost is another prostaglandin analogue very similar to Misoprostol, but because it is unstable it needs refrigeration, additionally it is more expensive and may only be administered vaginally [25]. Misoprostol is widely available and has low cost. Generally the effect of medical methods of abortion depending on uterine cramping, cervical dilatation, prolonged menstrual like bleeding with duration 9 days on average and only in rare cases up to 45 days. Side effects include nausea, vomiting and diarrhea. Among contraindications are: chronic adrenal hepatic failure, inherited porphyria and allergy. Clinical judgement is required in cases using corticosteroid for a long time [26]. For selection of the medical abortion as most appropriate method is important the following points: determination of pregnancy length, confirmation of intrauterine pregnancy, the exclusion of ectopic pregnancy (occurrence 1.5–2% of pregnancies). In suspicious cases like previous ectopic pregnancy, pelvic inflammatory disease and pregnancy in the presence of an intrauterine device, further examinations as vaginal ultrasound and serial human chorionic gonadotropin measurements are necessary [26,27]. To avoid failed termination of pregnancy is of great importance not the procedure undertaken at a very early gestation age. Otherwise the decidua only be evacuated and the conceptus be not dislodged [26,27].

An anembryonic pregnancy is a special case of missed abortion where fetal development fails at a very early stage of pregnancy. The embryonic sac continues to develop but there is no evidence of embryo in the ultrasound. The term missed abortion refers to a pregnancy where endometrial death happened before the 20th week of gestation but the embryo has not been miscarriage. Thus, if spontaneous abortion has not occurred, and if it is not desirable to wait, it is indicated the administration of Misoprostol in order to avoid surgical abortion. Misoprostol has been shown to be very effective in uterine emptying in cases of anembryonic pregnancy or fetal death [28–31].

The active metabolite from misoprostol is misoprostol acid

that induces contractions of the uterus and cervical ripening, opening which led to expulsion of pregnancy. Oxytocin increases the contractility of the uterus but is not in itself capable of to lead to cervical maturation. Oxytocin receptors are found in myometrium and out of pregnancy, however, receptor protein mRNA begins to be detected at 13 weeks of gestation and increases during pregnancy reaching levels 300 times higher than out-of-pregnancy levels [32].

Oxytocin receptors are at their highest concentration at the fundus of the uterus.

The bioavailability of misoprostol is diminished by the simultaneous consumption of food or anti-acid drugs. It is firstly metabolized in the liver, it does not interact with other drugs and less than 1% of its active metabolite is secreted in the urine. Although the company producing it does not accord to this use and its use has not been officially approved. Experience is adequate to administer it for first-trimester medical abortion and preparation of the cervix for surgical termination of the pregnancy [32].

Misoprostol depending on the route of administration (oral, vaginal, rectal) shows different pharmacokinetics. Blood levels reach their maximum serum concentration according to a Khan study after 10 min sublingual, 30 minutes of oral, 60 minutes buccal, 65 minutes vaginally and finally at 71.7 minutes after rectal administration [33].

Mifepristone is known as abortion pill, firstly approved for abortion beyond the 1st trimester in 1994; formerly called RU-486 is a hormone blocking the progesterone receptors. Mifepristone is associated with 5 to 8 fold greater binding affinity to progesterone receptor compared to progesterone, inhibiting the action of progesterone and interfering with the continuation of pregnancy [34–36]. The above mentioned medical agent is obligatory to be taken orally and its clinical effect begins 12–14 hours after intake and reach the maximal effect at 36–48 hours. There are two types of antiprogesterone preparation, the first one Trilostane has inhibited effect to progesterone synthesis and the second one is Mifepristone which comprises progesterone blocking compounds [37–39]. Side effects relate to a few and mild suppression of adrenocortical hormones. Mifepristone, was produced in 1980 and was used for the first time in France in 1987. [37–39]. Mifepristone has high affinity with intracellular receptors of progesterone and glucocorticosteroids, as a consequence it competes them for binding. The phenylaminodimethyl group at the 11 β site reacts with a specific region at the receptor binding site and causes structural qualifications [37–39]. It is a drug, taken per os, generally used in combination with Misoprostol to provoke an abortion. This combination is more than 95% adequate during the first trimester of pregnancy. It is less efficient in the second trimester of pregnancy. In clinical practice, there are various dosing protocols. Generally, the efficacy of the method should be confirmed by transvaginal ultrasound two weeks after use [37–39]. Frequent side effects include abdominal pain, tiredness and vaginal bleeding. Severe side effects may involve massive vaginal bleeding, bacterial infection and congenital abnormalities of the fetus if pregnancy is not

terminated. If used, proper care should be taken. Mifepristone is an antiprogesterone that acts by inhibiting the effects of progesterone and provoking uterine contractions. Mifepristone is in the World Health Organization's list of the most effective and secure medicines needed in a healthcare system and was the first drug which was used to stop a gestation [37-39].

A safe option to surgical miscarriages is the misoprostol that can be applied alone or in combination with other drugs (such as mifepristone). Medical abortion has the benefit of being less invasive, better accepted by women and more discreet. It is desirable for some, because the drugs usually cause miscarriage and surgical intervention is rarely required. The World Health Organization provides clear and easily accessible guidelines about how to use, the benefits compared to other methods, and the potential risks of misoprostol when used to induce abortion. There are also local guidelines that differ and are tailored to different needs depending on the country [40-42]. As will be shown in this paper, misoprostol is more effective when used in combination with mifepristone than used as a monotherapy, that's why there are several protocols for the combination of the two drugs. 1% of women who undergo medical abortion with misoprostol may present severe haemorrhage requiring medical care or hospitalization [40-42]. Some women may have an ectopic pregnancy that could be diagnosed prior to treatment. There are pregnancies that continue after misoprostol administration as a failure of the method. 12% of these embryos are more likely to have congenital abnormalities. For this reason, a more effective abortion method usually follows, such as uterine curettage. So, it is necessary to inform the woman, that although complete abortion is not certain, stopping pregnancy after the application is recommended [40-42]. Misoprostol can also be used to prepare the cervix, before the surgical abortion. There are indications that the all procedure is facilitated, while later complications from cervical trauma such as premature births are reducing. Especially effective is when misoprostol is applied in the second trimester, where it can be combined with cervical dilation such as Lamical or Dilapan. In any case, we have to think about the possibility of next pregnancy and to protect in every way the woman's genital system [40-42].

Nowadays, misoprostol's role is so important that is included into the World Health Organization's List of Essential Medicines [43-44]. In the 1990s, a gestation discontinuation with misoprostol combined with abortion drugs took place successfully in approximately three million women. Many authors report that the simultaneous administration of misoprostol with either methotrexate or mifepristone has high efficacy for the first trimester termination of pregnancy, with results ranging from 83% to 96% for the combination of methotrexate and misoprostol and 92% to 96% for the combination of misoprostol and mifepristone [45-48].

Mifepristone is an antagonist of progesterone receptors and is administered at a 600 mg oral dose or another 200 mg oral combination in combination after 36 hours of two doses of misoprostol 400 micrograms per dose transvaginal [45-48]. According to another study, 200 mg mifepristone was administered oral in combination with 800 mcg/ml

subcutaneously or transvaginal. Studies on the metabolism of mifepristone concluded that no significant differences in blood concentrations within 48 h of administration with oral doses ranging from 100 to 800 mg without any influence to the safety and efficacy [49-52]. Induced abortions were performed in pregnancies of less than 49, 50-56, 57-63 days or <9 weeks [53-54].

Mifepristone combined with a prostaglandin analogue (misoprostol or gemeprost) is a treating option extensively used for medical abortions. During the years, this combination has been proven to be safe and effective. Guidelines from Royal College of Obstetricians and Gynecologists characterize this treatment option as an effective and proper method of terminating pregnancy. In contrary, the monotherapy with mifepristone is less effective, resulting in abortion only in 8% to 46% of pregnancies within 1-2 weeks. This is the cause it is almost always used in combination with misoprostol [55]. Mifepristone in combination with other drugs, is also used as treatment of hyperglycaemia caused by high levels of cortisol in adults with endogenous Cushing's syndrome who have diabetes mellitus type 2 or glucose intolerance and have failed to surgery or cannot undergo surgery [56]. Mifepristone can also be used for emergency contraception, although its use is not widespread [57].

Abdominal pain, uterine cramps and vaginal bleeding for nine to sixteen days are referred by almost all women who used the mifepristone/misoprostol regimen. Up to 8% of women have showed some kind of bleeding for 30 or more days. Among the less common side effects are referred nausea, vomiting or tendency to vomit, diarrhoea, dizziness, fatigue and fever [58-60]. Pelvic inflammatory disease is a serious but not very often complication. Massive bleeding and inadequate emptying of uterine cavity require further management (such as endometrial ablation surgery) and sometimes hospitalization. Mifepristone is clearly contraindicated in ectopic pregnancy, adrenal insufficiency, bleeding disorders, hereditary porphyria, and long-term corticosteroid therapy [61,62]. Always some pregnancies have been undesirable. Many times, either because of rape, career, or economic reasons, women or their families considers this pregnancy unwanted [61,62]. Historically there have been several ways for an unwanted pregnancy to end. Some of them unfortunately were dangerous to the health and life of the pregnant woman [61,62]. Clearly the best treatment for unwanted pregnancy is to avoid it. With the advancement of family planning and contraception, the greatest number of unwanted pregnancies should be avoided. Unfortunately this is not always feasible. However, we must emphasize that every euro given to prevention dramatically reduces health care costs for complications and the treatment of infertility [61,62].

There were ways of limiting the woman, who wants to end a pregnancy. The prohibition of abortion, apart from the fact that it is considered a limitation of women's rights, is associated with an increase in illegal abortions. This increase hides major dangers for women's health and life, such as septicemia and peritonitis. Damage to society is, on the one hand, the immediate need to cover hospitalization, on the other hand, clearly greater and longer-term health cover in the

event of disability or death [63,64]. In most Islamic countries abortion is forbidden and there are very severe penalties (up to death penalty) for any woman trying to end an unwanted pregnancy. The problem is more than doubled and the fact that not all methods of contraception are acceptable to the Koran. With the rise of Muslims in Europe, it is increasingly necessary for doctors of European countries to deal with cases that were considered outdated decades ago [63,64]. There are Catholic countries in both Latin America and Europe, where there is a total or partial ban on abortion.

In some countries in Europe, such as Ireland and Malta, abortion is forbidden even when the embryo has abnormalities, even in cases of rape or incest. In most European countries abortion is permitted in some cases (embryo abnormalities, maternal disability, social reasons, as well as rape and incest). In some countries such as Greece, Bulgaria, Denmark, France, Germany, Austria, the Czech Republic, Slovenia, Slovakia, Sweden, Spain, Portugal, Estonia, Latvia, Lithuania and Luxembourg mother abortions are also permitted. In Italy, Poland, Hungary, the Netherlands and Belgium abortion is prohibited [63,64].

With advances in medicine over the last decades, endometrial abortion was predominantly a method of ending unwanted pregnancies. Unfortunately, although it's pretty safe, neither is this method perfect. Some of its disadvantages are that it requires in-patient care, sometimes hospitalization, and increased costs. As a surgical operation, curettage also carries the risk of uterine and endometrial injury. There are only a few cases that women have infertility problems after scraping [63,64].

As the newspaper First Subject writes on June 12, 2015 - 40,000 abortions per year in our country are decided by girls under the age of 18.5. In women under the age of 20 for social reasons, the chance of recourse to illegal abortion is even greater. There are few cases when these girls follow the advice of friends or get instructions via the Internet trying to end pregnancy with methods dangerous and outdated for centuries. The possibility of suicide should also be assessed in extreme cases.

Historically and politically, the Church is very important for Greece. Although judiciary and justice are not always in accordance with ethics, the role of the Church in shaping public opinion is crucial. The dialogue on whether or not to ban abortion in Greece is open. The position of the Orthodox Church is clear, expressing an important part of the society as a whole, according to which "embryonic life, as a born human life, is qualitatively equal, or not substantially, different from that of man." The embryo is an autonomous existence for the Church that fits in with an independent criminal protection, independent of that reserved for the physical integrity of the woman.

Medical termination of pregnancy is a relatively safe procedure associated to low overall mortality less than 2 per 100000 and low morbidity [63,64]. Early complications include retained products of conception (04%-2.9%), hemorrhage,

and long term following medical procedure as following: pelvic inflammatory disease and subfertility subsequent light for dates infants, ectopic pregnancy due to inflammation, psychiatric sequel [63,64]. In our collective were noticed only simple complications without necessity of hospital stay. To prevent pain and abdominal cramps occurrence depending on prostaglandin induced uterine contractions was recommend and administrated prophylactic NSAIDS (non-steroidal antiinflammatory drugs like paracetamol, ibuprofen) and in rare severe pain cases codeine, tramadol, diazepam. NSAIDS have a block effect in the biosynthesis of endogenous prostaglandins and no in the exogenously administrated prostaglandins. Antibiotic treatment was used for all pregnant participants up to 7 days after starting medication.

Pregnant women who are contemplating abortion should be adequate informed, counseling from a competent trained professional health care in family planning centers with great experience and comprehensive knowledge relate to various methods of abortion. The family planning centers must be provided information to each woman regardless from age, religion or circumstances in a way that she understand to allow the adequate choice and decision about the whether to have abortion and the suitable method. Information, counseling and abortion procedures should be provided as promptly as possible without undue delay due to greater safety at earlier gestational ages. According to our results and in conformance to international literature is medical abortion safe and effective in first trimester and compared to surgical curettage be avoid cervical damage, uterine perforation, hemorrhage, sepsis (incidence in surgical procedure 0.4-4.8%, 0.04-1.7%, 6%, 5% respectively). Based on our findings the contribution of mifepristone as well alone in the early terminations Group A1 as in combination with misoprostol in the late terminations Group B1 is very important to led earlier to beginning of bleeding, abortion and short the time between medical administration and total expulsion compared to misoprostol alone in the both groups (Table2,5). Side effects rate in our study participants was low and similar to the control groups with misoprostol administration (Table 3,6). The reported failure rate in the international literature range 0.5-15% [63,64]. The absolutely majority of our study cases were not underwent in surgical procedures and needed hospitalization except for twelve cases, nine in the Group B2 and three in the Group B1. All these cases reported various methods of uterine surgery and installed placental tissue in the ultrasound. These cases were admitted in hospital, underwent in fractional curettage and in the same day of admission became exit from hospital stay and went back to home without problems. Also is our failure rate by 3/200 (1.5%) Group A1, and by 9/200 (4.5%) GroupB1. In the follow up period performed within two weeks of abortion we not found residual tissue of placenta and not noticed any complications either related to intrauterine cavity or infection, serious post abortion vaginal bleeding and menstruations changes.

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methods of abortion. The family planning centers must be provided information to each woman regardless from age religion or circumstances in a way that she understand to allow the adequate choice and decision about the whether to have abortion and the suitable method. Information, counseling and abortion procedures should be provided as promptly as possible without undue delay due to greater safety at earlier gestational ages.

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